

INTERNATIONAL SEARCH REPORT

International Application No.

US2004/020536

A. CLASSIFICATION OF SUBJECT MATTER

A61K9/127 A61K31/663 A61K9/51

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)

A61K

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data, EMBASE, BIOSIS, MEDLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	US 2002/187184 A1 (GOLOMB GERSHON ET AL) 12 December 2002 (2002-12-12)	42-63
Y	page 1, paragraph 6 - page 2, paragraph 9 page 3, paragraph 30-36 page 5, paragraph 58 - page 6, paragraph 63 claims 1-34	1-41, 64-69
X	US 2002/192157 A1 (LOW PHILIP S ET AL) 19 December 2002 (2002-12-19)	42-63
Y	page 5 - page 6; example 3 page 7; example 10 claims 1-19	1-41, 64-69

-/-

☒ Further documents are listed in the continuation of box C.☒ Patent family members are listed in annex.

* Special categories of cited documents:

A document defining the general state of the art which is not considered to be of particular relevance

E earlier document but published on or after the international filing date

L document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)

O document referring to an oral disclosure, use, exhibition or other means

P document published prior to the international filing date but later than the priority date claimed

T later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention

X document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone

Y document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art

Z document member of the same patent family

Date of the actual completion of the international search

8 December 2005

Date of mailing of the international search report

23/12/2005

Name and mailing address of the ISA

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C. (Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category	Description of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	DE 196 37 890 A (MAX PLANCK GESELLSCHAFT) 19 March 1998 (1998-03-19)	42-63
Y	the whole document	1-41, 64-69
Y	TASHIRO ET AL.: "Monocyte-related cytokines in acute myocardial infarction" AMERICAN HEART JOURNAL, vol. 130, no. 1, 1995, pages 446-452, XP002358123 page 446 page 448, column 2, line 17 - page 449, column 1, line 4	1-41, 64-69

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2004/020536

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
Although claims 1-41, 64-69 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No.

US2004/020536

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
US 2002187184	A1	12-12-2002	NONE
US 2002192157	A1	19-12-2002	NONE
DE 19637890	A	19-03-1998	NONE

PCT

To:

see form PCT/ISA/220

WRITTEN OPINION OF THE
INTERNATIONAL SEARCHING AUTHORITY
(PCT Rule 43bis.1)

Date of mailing
(day/month/year) see form PCT/ISA/210 (second sheet)

Applicant's or agent's file reference
see form PCT/ISA/220

FOR FURTHER ACTION
See paragraph 2 below

International application No.
PCT/US2004/020536

International filing date (day/month/year)
24.06.2004

Priority date (day/month/year)
27.06.2003

International Patent Classification (IPC) or both national classification and IPC
A61K9/127, A61K31/663, A61K9/51

Applicant
BIOREST LTD.

1. This opinion contains indications relating to the following items:

- ☒ Box No. I Basis of the opinion
- ☐ Box No. II Priority
- ☒ Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- ☐ Box No. IV Lack of unity of invention
- ☒ Box No. V Reasoned statement under Rule 43bis.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
- ☐ Box No. VI Certain documents cited
- ☐ Box No. VII Certain defects in the international application
- ☐ Box No. VIII Certain observations on the international application

2. **FURTHER ACTION**

If a demand for international preliminary examination is made, this opinion will usually be considered to be a written opinion of the International Preliminary Examining Authority ("IPEA"). However, this does not apply where the applicant chooses an Authority other than this one to be the IPEA and the chosen IPEA has notified the International Bureau under Rule 66.1bis(b) that written opinions of this International Searching Authority will not be so considered.

If this opinion is, as provided above, considered to be a written opinion of the IPEA, the applicant is invited to submit to the IPEA a written reply together, where appropriate, with amendments, before the expiration of three months from the date of mailing of Form PCT/ISA/220 or before the expiration of 22 months from the priority date, whichever expires later.

For further options, see Form PCT/ISA/220.

3. For further details, see notes to Form PCT/ISA/220.

Name and mailing address of the ISA:



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Box No. I Basis of the opinion

1. With regard to the **language**, this opinion has been established on the basis of the international application in the language in which it was filed, unless otherwise indicated under this item.
 - ☐ This opinion has been established on the basis of a translation from the original language into the following language , which is the language of a translation furnished for the purposes of international search (under Rules 12.3 and 23.1(b)).
2. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this opinion has been established on the basis of:
 - a. type of material:
 - ☐ a sequence listing
 - ☐ table(s) related to the sequence listing
 - b. format of material:
 - ☐ in written format
 - ☐ in computer readable form
 - c. time of filing/furnishing:
 - ☐ contained in the international application as filed.
 - ☐ filed together with the international application in computer readable form.
 - ☐ furnished subsequently to this Authority for the purposes of search.
3. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.
4. Additional comments:

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non obvious), or to be industrially applicable have not been examined in respect of:

- ☐ the entire international application,
- ☒ claims Nos. 1-41,64-69, with respect to industrial applicability

because:

- ☐ the said international application, or the said claims Nos. relate to the following subject matter which does not require an international preliminary examination (*specify*):
- ☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. are so unclear that no meaningful opinion could be formed (*specify*):
- ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.
- ☒ no international search report has been established for the whole application or for said claims Nos. 1-41,64-69, with respect to industrial applicability
- ☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:
 - the written form ☐ has not been furnished
 - ☐ does not comply with the standard
 - the computer readable form ☐ has not been furnished
 - ☐ does not comply with the standard
- ☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-bis of the Administrative Instructions.
- ☐ See separate sheet for further details

Box No. V Reasoned statement under Rule 43*bis*.1(a)(i) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-41,64-69
	No: Claims	42-63
Inventive step (IS)	Yes: Claims	
	No: Claims	1-69
Industrial applicability (IA)	Yes: Claims	42-63
	No: Claims	

2. Citations and explanations

see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

For the assessment of the present claims 1-41, 64-69 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

Re Item V

Reasoned statement with regard to novelty, inventive step and industrial applicability; citations and explanations supporting such statement

1. Cited Documents

The following documents are referred to in this communication:

- D1: US 2002/187184 A1 (GOLOMB GERSHON ET AL) 12 December 2002 (2002-12-12)
- D2: US 2002/192157 A1 (LOW PHILIP S ET AL) 19 December 2002 (2002-12-19)
- D3: DE 196 37 890 A (MAX PLANCK GESELLSCHAFT) 19 March 1998 (1998-03-19)
- D4: TASHIRO ET AL.: "Monocyte-related cytokines in acute myocardial infarction" AMERICAN HEART JOURNAL, vol. 130, no. 1, 1995, pages 446-452, XP002358123

2. Clarity objection

The terms "intra-cellular inhibitor", "intra-cellular deactivator", "intra-cellular arrestor", "intra-cellular toxin", "cytostatic substance", and "cytotoxic substance" used in claims 45-50 do not clearly identify the agents and do not inform the skilled man of their exact nature.

Therefore, claims 45-50 are unclear (Article 6 PCT).

3. Lack of support

The present set of claims relates to an extremely large number of possible formulations comprising an encapsulated agent, an embedded agent or a particulate agent. Support within the meaning of Article 6 PCT is to be found, however, for only a very small proportion of the formulations claimed, namely bisphosphonates encapsulated in liposomes.

4. Novelty

D1 discloses (see claims 1-34) a method of treating or preventing restenosis by administering an active compound which depletes and/or inhibits blood monocytes or macrophages. Preferred compounds are bisphosphonates such as clodronate or other inactivators of monocytes/macrophages such as gallium. The compounds can be encapsulated in a liposome or embedded in micro- or nanoparticles. The subject-matter of claims 42-63 is therefore not new (Article 33(2) PCT).

D2 discloses (see example 3 on pages 5,6) the use of liposomes comprising clodronate and having a size < 100 nm as intraperitoneal injection for macrophage depletion. The subject-matter of claims 42-52,55-63 is therefore not new (Article 33(2) PCT).

D3 discloses a liposomal medicament comprising a bisphosphonic acid salt as active agent, contained in a liposomal shell consisting of cholesterol, DPPC, and DPPA in a ratio of 1-2:2-6:1-3. The liposomes having an average size < 100 nm can be injected intravenously and can be used for decreasing vascular repulsion of organs, by vascular elimination of monocytes. The subject-matter of claims 42-52,55-63 is therefore not new (Article 33(2) PCT).

5. Inventive Step

As disclosed in D4, the role of monocytes/macrophages in acute myocardial infarction is well known in the art.

Consequently, it appears the person skilled in the art would have used the abovementioned formulations disclosed in D1-D3, which inhibit or deplete monocytes/macrophages, for the treatment of acute myocardial infarction.

Claims 1-41, 64-69 therefore do not appear to satisfy the criteria of inventive step (Article 33(3) PCT).

6. Industrial applicability

Claims 1-41, 64-69 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Claims 42-63 satisfy the criterion of industrial applicability set forth in Article 33(4) PCT.